European Journal of Neuroscience, Vol. 21, pp. 1000–1006, 2005

Exposure to pulse-modulated radio frequency electromagnetic fields affects regional cerebral blood flow

R. Huber,[1] V. Treyer,[2] J. Schuderer,[3] T. Berthold,[2] A. Buck,[3] N. Kuster,[3] H. P. Landolt[1] and P. Achermann[1]
[1]Institute of Pharmacology and Toxicology, University of Zurich, Zurich, Switzerland
[2]PET Center, Division of Nuclear Medicine, University Hospital, Zurich, Switzerland
[3]Foundation for Research on Information Technologies in Society (IT'IS), Zurich, Switzerland

Keywords: cellular phone, electromagnetic fields, global system for mobile communication (GSM), positron emission tomography

Abstract

We investigated the effects of radio frequency electromagnetic fields (RF EMF) similar to those emitted by mobile phones on waking regional cerebral blood flow (rCBF) in 12 healthy young men. Two types of RF EMF exposure were applied: a 'base-station-like' and a 'handset-like' signal. Positron emission tomography scans were taken after 30 min unilateral head exposure to pulse-modulated 900 MHz RF EMF (10 g tissue-averaged spatial peak-specific absorption rate of 1 W/kg for both conditions) and sham control. We observed an increase in relative rCBF in the dorsolateral prefrontal cortex on the side of exposure. The effect depended on the spectral power in the amplitude modulation of the RF carrier such that only 'handset-like' RF EMF exposure with its stronger low-frequency components but not the 'base-station-like' RF EMF exposure affected rCBF. This finding supports our previous observation that pulse modulation of RF EMF is necessary to induce changes in the waking and sleep EEG, and substantiates the notion that pulse modulation is crucial for RF EMF-induced alterations in brain physiology.

Introduction

Increasing evidence suggests that pulse-modulated, radio frequency electromagnetic fields (RF EMF) alter brain physiology. We have found consistent effects of RF EMF emitted by mobile phones in the human non-rapid eye movement (REM) sleep electroencephalogram (EEG; Borbély *et al*., 1999; Huber *et al*., 2000, 2002, 2003). More recently, RF EMF were shown to also affect the waking EEG (Croft *et al*., 2002; Huber *et al*., 2002) and waking regional cerebral blood flow (rCBF; Huber *et al*., 2002). In another line of research, RF EMF were reported to influence cognitive functions (Preece *et al*., 1999; Koivisto *et al*., 2000a,b) and attention (Edelstyn & Oldershaw, 2002). In recent studies, however, previously reported changes in cognitive functioning could not be replicated (Haarala *et al*., 2003b; Krause *et al*., 2004). Also, the analysis of event-related brain potentials during RF EMF exposure revealed conflicting results (Eulitz *et al*., 1998; Freude *et al*., 1998; Jech *et al*., 2001). It is possible that some inconsistencies are related to the spectral content of the applied RF EMF. Most studies did not investigate different spectral compositions of the emitted RF radiation. Nevertheless, we recently found that pulse modulation of the RF EMF is necessary to induce changes in the EEG in waking and sleep (Huber *et al*., 2002). In addition, the changes in non-REM sleep induced by a 'base-station-like' RF EMF (Borbély *et al*., 1999; Huber *et al*., 2000) mimicked only partly, but not entirely, the changes induced by a 'handset-like' RF EMF (Huber *et al*., 2002).

A first analysis restricted to 'handset-like' RF EMF and sham exposure revealed increased relative rCBF in the dorsolateral prefrontal cortex (PFC) ipsilateral to the side of exposure (Huber *et al*., 2002). In the present study, we additionally investigated the effect of a 'base-station-like' signal on local rCBF and compared it with a 'handset-like' signal. We hypothesized that alterations in rCBF would either be stronger or even restricted to exposure to 'hand-set like' RF EMF. To help interpret our findings we compared the changes in rCBF with the simulated specific absorption rate (SAR) distribution of the applied RF EMF within the brain.

Materials and methods

Sixteen healthy, right-handed men (mean age 22.5 years, range 20–25 years) participated in the study. Written informed consent was obtained prior to the experiment and a specialized ethical committee of the Canton of Zurich for research on human subjects approved the study protocol. Subjects were instructed to abstain from caffeine, alcohol and medication, and to keep a regular sleep–wake schedule (8 h sleep starting not later than midnight) on the day prior to the study. Compliance with the latter instruction was verified by wrist-worn activity monitors. The use of mobile phones was not allowed on the day of the experiment.

Prior to positron emission tomography (PET) data acquisition, the subjects' left hemisphere of the brain was exposed for 30 min to RF EMF (same exposure unit as described in Huber *et al*., 2000, 2002). During exposure the subjects sat on a chair with their heads positioned between two planar antennas to ensure a well-defined exposure (for details of the setup, see Huber *et al*., 2003). With this setup, exposure is less localized compared with using a mobile phone. It covers, however, all head tissues that may be exposed using different mobile phones operating in the 800–900 MHz bands and due to different phone positions at the ear. The time-averaged maximum local exposure corresponds to that of an average cellular GSM (global

Correspondence: Dr R. Huber, Psychiatry Department, University of Wisconsin, 6001 Research Park Boulevard, Madison, WI 53719, USA.
E-mail: rhuber@facstaff.wisc.edu

Received 20 July 2004, revised 9 November 2004, accepted 8 December 2004

doi:10.1111/j.1460-9568.2005.03929.x

system for mobile communication) phone. The setup fulfils the requirements of EMF exposure in human studies in the context of health risk assessments of mobile phones (Kuster *et al*., 2004).

The time between the end of exposure and the first PET scan was 10 min, the time needed to place the subjects on the PET scanner. RF EMF exposure was scheduled between 08.00 and 14.00 h. The experiment consisted of a double-blind (controlled by computer) sham-controlled (no RF EMF activated) cross-over design with two active conditions: a 'handset-like' signal (handset) and a 'base-station-like' (bstat) signal. The intervals between the exposure conditions were at least 1 week. The handset signal consisted of a generic signal with a similar spectral content as the one emitted by GSM mobile phones (Fig. 1; one of eight slots active, used in Huber *et al*., 2002). The bstat signal consisted of a signal that mimicked the signal modulation emitted by a GSM base station (Fig. 1; seven of eight slots of the basic frame active, used in Borbély *et al*., 1999; Huber *et al*., 2000). Both signals were applied at a carrier frequency of 900 MHz. A detailed description of the signal is given in Fig. 1. It is important to note the following. (i) The strength and distribution of the time-averaged RF EMF absorption in the tissue were identical for both exposure conditions. The spatial peak SAR averaged over 10 g of tissue was 1 W/kg for both conditions, which is similar to the maximum exposure induced by commercial GSM phones (Kuster *et al*., 1997). (ii) Both signals had the same spectral components. (iii) The handset signal had considerably higher power in the main spectral components, i.e. at 2, 8, 217, 1736 Hz and in their harmonics. The crest factor (ratio between pulse peak power and time-averaged power) differed by a factor of four, i.e. it was 1.2 for the bstat signal and 4.8 for the handset signal.

The exposure conditions were well controlled and characterized by a detailed dosimetry (assessment of dosimetric measurement uncertainty, variations due to head movements, differences in anatomy, etc, see Huber *et al*., 2003). The 10 g tissue-averaged spatial peak SAR was 1.0 W/kg ± 14% (%-value covers uncertainty of the dosimetric assessment as well as exposure variations). The average SAR in the exposed brain hemisphere was 6.7 times higher than in the non-exposed hemisphere, i.e. about 0.27 W/kg ± 23% vs. 0.04 W/kg ± 23%. The maximum 1 g tissue-averaged spatial peak SAR in the brain was 1.5 W/kg ± 23%.

The PET data acquisition was previously described in detail (Huber *et al*., 2002). In short, three PET emission scans were recorded at 10-min intervals after administration of 300–350 MBq radio-labelled water. A 10-min transmission scan completed the data acquisition. During the scans subjects were instructed to silently count slowly from 1 to 60 to ensure similar cognitive activity in all conditions. We chose an over-learned control task to minimize learning and to prevent interactions of EMF exposure with higher cognitive functions. Data were reconstructed into 35 image planes (slice thickness, 4.25 mm; matrix, 128 × 128; pixel size, 2.34 mm). The accumulated radioactivity counts over 60 s were taken as a measure of cerebral blood flow. Statistical analysis of the data was performed using statistical parametric mapping (SPM99) software. Prior to statistical evaluation, preprocessing was performed as follows. First, head movements within-subject and between data acquisition sessions (three scans per session, three separate sessions) were corrected using the least-squares method implemented in the SPM99 software (Friston *et al*., 1995). Then the scans were spatially normalized into stereotactic space [Montreal Neurological Institute (MNI) coordinates as provided by SPM99] and smoothed with a 15 mm Gaussian filter to ameliorate residual interindividual anatomical and functional differences after spatial normalization. Statistical analysis was performed on proportionally scaled data including all individual scans of the same condition as repetitions. For each scan the voxel values were normalized to the mean of the whole brain grey matter activity. Differences between the conditions were tested on a voxel-by-voxel basis in a PET multisubject design. The results were corrected for multiple comparisons with a threshold of $P < 0.05$ (SPM99, whole brain correction). MNI coordinates as provided by the SPM99 software are reported. For the anatomical localization of significant changes the Talairach daemon was used (http://ric.uthscsa.edu/projects/talairachdaemon.html). Because the daemon is based on Talairach coordinates, MNI coordinates were non-linearly transformed to Talairach coordinates (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html). Furthermore, a volume of interest (VOI) analysis was performed. VOI were defined based on SPM statistics. The following cut-off was used to define the extent of the VOI: Clusters of voxels with a *t*-value equal or larger than 5 formed a VOI. For the comparison between the two hemispheres the raw images were mirrored by swapping sides, realigned and spatially normalized to obtain normalized images with the right hemisphere on the left side. This extra processing step was introduced as the two hemispheres on the used MNI template were not symmetric. Using the same VOI definitions from the right hemisphere on the mirrored images revealed the VOI values for the left hemisphere. The mirroring did not introduce any visible error. VOI were analysed for hemispheric differences and temporal changes of the effect of RF EMF exposure using three-way ANOVAs with within-factor 'hemisphere' (left, right), within-repeated-factor 'time' (10, 20 and 30 min after exposure) and between-factor 'order' [SAS procedure MIXED (type hf); SAS Institute Inc, 1999].

Because of technical problems and logistical reasons, only 12 subjects completed all three conditions and the order of conditions was not balanced. The factor order was included in the statistics of the VOI to assess whether our results were affected by the order of the conditions. No significant order effect or interactions involving order were observed. To further test for order effects we performed a factorial analysis (SAS procedure DISCRIM, SAS Institute Inc, 1999) including all individual data points. No statistical significant separation of the data into groups with the same order of conditions was observed. The effects of handset RF EMF exposure in relation to sham exposure have been reported previously (Huber *et al*., 2002).

Results

RF EMF exposure affected relative rCBF in the hemisphere of exposure (Table 1, Fig. 2). The effect varied with the modulation scheme. Mainly handset exposure altered rCBF (handset compared with sham or bstat; Table 1). The bstat compared with the sham condition did not result in any significant change in rCBF.

Both *handset–sham* and *handset–bstat* contrasts revealed increased relative rCBF after handset exposure in the left inferior frontal gyrus [Brodmann areas (BA) 9 and 44]. In addition, increased rCBF was observed in the left middle frontal gyrus in BA 6, postcentral gyrus in BA 2 (*handset–sham* contrast), and in BA 10 and 40 (*handset–bstat* contrast). Handset exposure compared with the sham condition (*sham–handset* contrast) indicated reduced rCBF in the right posterior lobe of the cerebellum (1 voxel).

In the right inferior temporal gyrus in BA 20, rCBF increased after bstat exposure compared with the handset exposure.

The changes in rCBF after exposure did not correspond with the simulated distribution of the SAR (Fig. 2). Although the changes in rCBF coincided with brain areas with high levels of exposure, the regions that were exposed were much larger than those showing significant changes in rCBF.

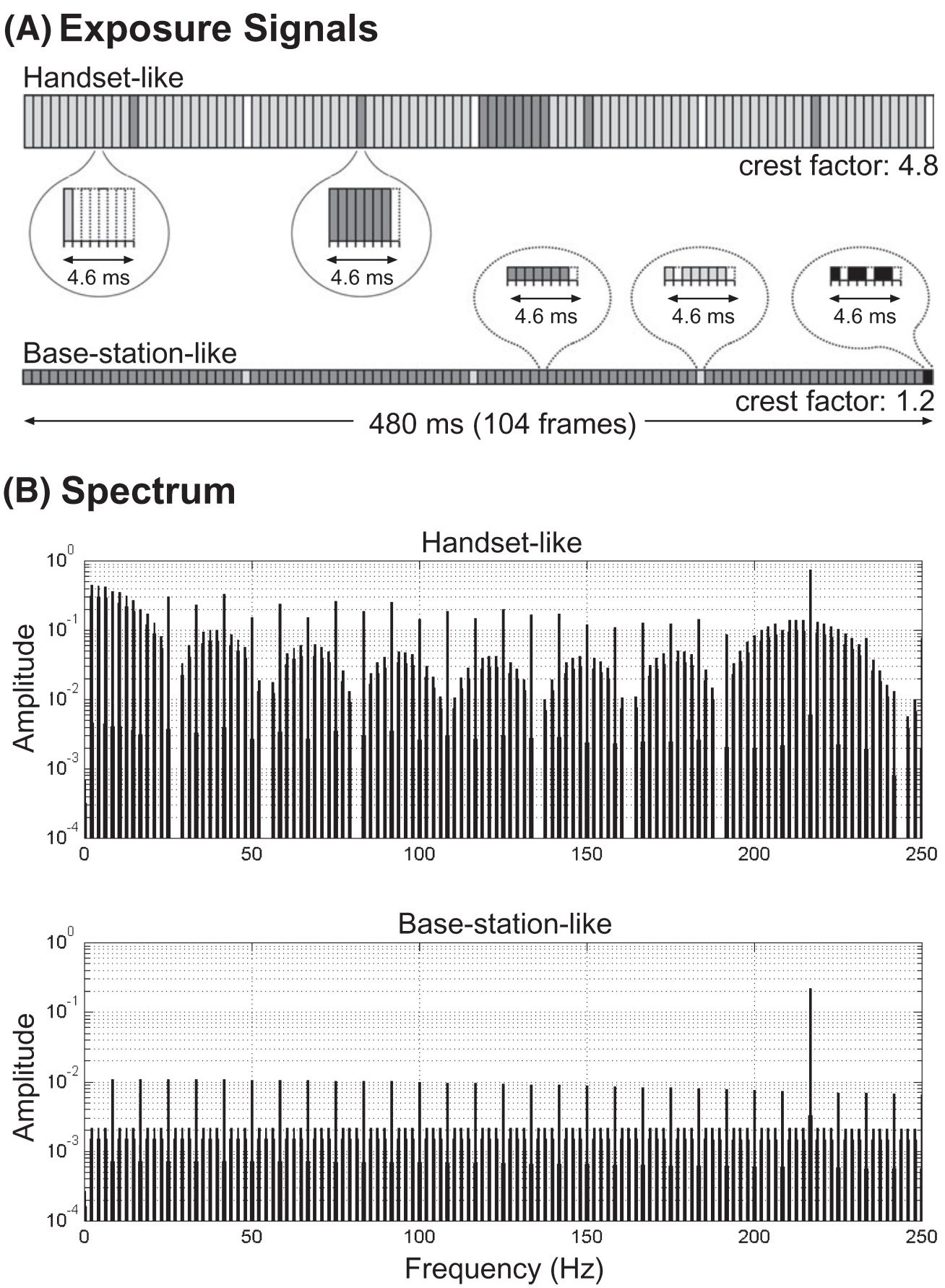
(A) Exposure Signals
Handset-like
crest factor: 4.8
4.6 ms
4.6 ms
4.6 ms
4.6 ms
4.6 ms
Base-station-like
crest factor: 1.2
480 ms (104 frames)
(B) Spectrum
Handset-like
Amplitude
Base-station-like
Amplitude
Frequency (Hz)

TABLE 1. Effect of RF EMF exposure on relative rCBF: SPM statistic

			MNI coordinates			Voxel level		Cluster level	
	Region	H	*x*	*y*	*z*	*t*	P_{corr}	*k*	P_{corr}
Handset–sham									
Inferior frontal gyrus, BA 9 (3)	a	L	−40	6	36	5.85	< 0.001	99	0.002
Frontal lobe, subgyral, BA 6 (7)		L	−22	0	44	5.44	0.002	72	0.003
Inferior frontal gyrus, BA 44	b	L	−54	12	16	5.43	0.002	149	0.001
Postcentral gyrus, BA 2 (3)		L	−34	−32	44	4.66	0.037	4	0.033
Sham–handset									
Cerebellum, posterior lobe		R	30	−68	−24	4.61	0.044	1	0.043
Handset–bstat									
Middle frontal gyrus, BA 10 (7)	c	L	−32	40	16	5.66	0.001	234	< 0.001
Inferior frontal gyrus, BA 44	b	L	−54	10	16	5.13	0.007	302	< 0.001
Inferior frontal gyrus, BA 9	a	L	−52	4	32	5.10	0.008		
Inferior frontal gyrus, BA 10 (3)		L	−52	40	0	4.89	0.017	19	0.016
Supramarginal gyrus, BA 40 (3)		L	−40	−42	36	4.61	0.044	3	0.036
Bstat–handset									
Inferior temporal gyrus, BA 20	d	R	52	−10	−36	5.00	0.012	23	0.014

Brain regions showing changes in relative rCBF after RF EMF exposure (BA = Brodmann areas). The MNI coordinates from the statistical parametric mapping (SPM99) are reported. Where the voxel with the highest *t*-value did not lay in grey matter, the nearest grey matter location was detected using the Talairach option 'find nearest grey matter' (search diameter in mm is provided in parentheses after the Brodmann area). Voxels with significant corrected *P*-values and their corresponding *t*-values are presented. In addition, the number of expected voxels (*k*) and the corrected *P*-value (P_{corr}) on the cluster level are indicated [R = cluster in right hemisphere (H), L = cluster in left hemisphere]. An identifier (region; a–d) refers to the brain regions indicated in Table 2 and Fig. 2.

A VOI analysis revealed hemispheric differences (factor 'hemisphere') after handset exposure compared with both sham and bstat exposure (Table 2). Relative rCBF in the exposed, left inferior frontal gyrus was higher after handset exposure than in the same region on the right hemisphere. While the factor 'time' was not significant, a significant 'hemisphere' by 'time' interaction was found in the inferior frontal gyrus in BA 44 (Table 2). This region showed an increase of rCBF with time in the left hemisphere that was not present in the right hemisphere (Fig. 3). A similar, though not significant, increase in rCBF over time was also observed when comparing handset with sham exposure.

Discussion

Regional CBF was increased in several different regions of the left dorsolateral PFC after handset exposure when compared with both sham or bstat exposure. These results substantiate the findings of our previous report in which the analysis was restricted to the comparison of handset–sham exposure (Huber *et al*., 2002). The small differences in size and location of the rCBF between the two analyses may result from the fact that different subjects (only those whose data sets were complete) and different contrasts were included in the analyses. Consistently, however, hemispheric differences were observed such that rCBF was affected mainly in the exposed hemisphere. The bstat signal had the same time-averaged energy as the handset signal. Therefore, our observation that the effect was restricted to handset exposure cannot be explained by a thermal action of RF EMF. The data provide further evidence that the pulse modulation of the RF EMF is crucial to induce changes in brain activity. They are in accordance with our previous finding that a pulse-modulated RF EMF (handset), but not a continuous-wave RF EMF, affected the EEG during waking and sleep (Huber *et al*., 2002). It remains open, however, whether differences in the strength of certain low-frequency components (Fig. 1) or the difference in the crest factor may underlie the effects on rCBF. Stimulation frequency-dependent effects on brain activity were observed with transcranial magnetic stimulation (TMS) such that low-frequency stimulation (1 Hz) induced inhibition (Chen *et al*., 1997), whereas stimulation with higher frequencies induced activation (Pascual-Leone *et al*., 1994).

In our study we found the strongest changes in rCBF after RF EMF exposure in the left PFC. This region plays a major role in working memory (Rypma *et al*., 1999; Dade *et al*., 2001; Wagner *et al*., 2001). The ventromedial PFC supports functions involving the integration of information about emotion, memory and environmental stimuli (Wood & Grafman, 2003). The dorsolateral PFC is involved in the regulation of behaviour and the control of responses to environmental stimuli (Wood & Grafman, 2003). Single-pulse TMS over the left prefrontal cortex, but not at other stimulation sites, reduced reaction time in a two-back task (Mottaghy *et al*., 2003). Similar effects of left hemispheric RF EMF exposure on cognitive function were repeatedly reported, particularly in tasks with a high workload (Preece *et al*., 1999; Koivisto *et al*., 2000a, b). These findings could be related to the observed increase of rCBF in the PFC. On the other hand, recent

FIG. 1. (A) Pulse structures of the applied generic GSM signals. The 'handset-like' signal (handset) and 'base-station-like' (bstat) signal were composed to contain all spectral components of the GSM signal in the frequency range below 1 kHz. Both are based on the GSM frame structure of which the basic frame (4.6 ms) is composed of 8 (#0, …, 7) slots (0.576 ms). The pulse structure of the handset signal combines the frame structure of the basic GSM mode and the discontinuous transmission (DTX) mode (both modes are alternately active during an actual GSM conversation, depending on whether one is listening or talking), i.e. active pulses in every slot #0 except in every 26th frame (idle frame) and, in addition, active pulses in slots #1–6 of the frames used in the DTX mode. The bstat signal approximates the signal emitted by a GSM base station in communication with seven mobile phones. It is composed of active pulses in slots #0–6, whereas each frame 26th and 104th are modified. The ratio between pulse peak power and time-averaged power (crest factor) was four times higher for the handset signal (crest factor = 4.8) compared with the bstat signal (crest factor = 1.2). (B) Amplitude spectra. Amplitude spectra of the envelope of the emitted RF EMF power of handset and bstat signals. Both signals had a time-averaged value of 1 (see A). The spectra reflect the side bands of the modulated carrier frequency, which actually contains the signal power. The spectra were calculated with a Fast Fourier Transformation after application of a Hanning window. Most frequency components have considerably higher spectral amplitude (up to two orders of magnitude) in the handset signal compared with the bstat signal.

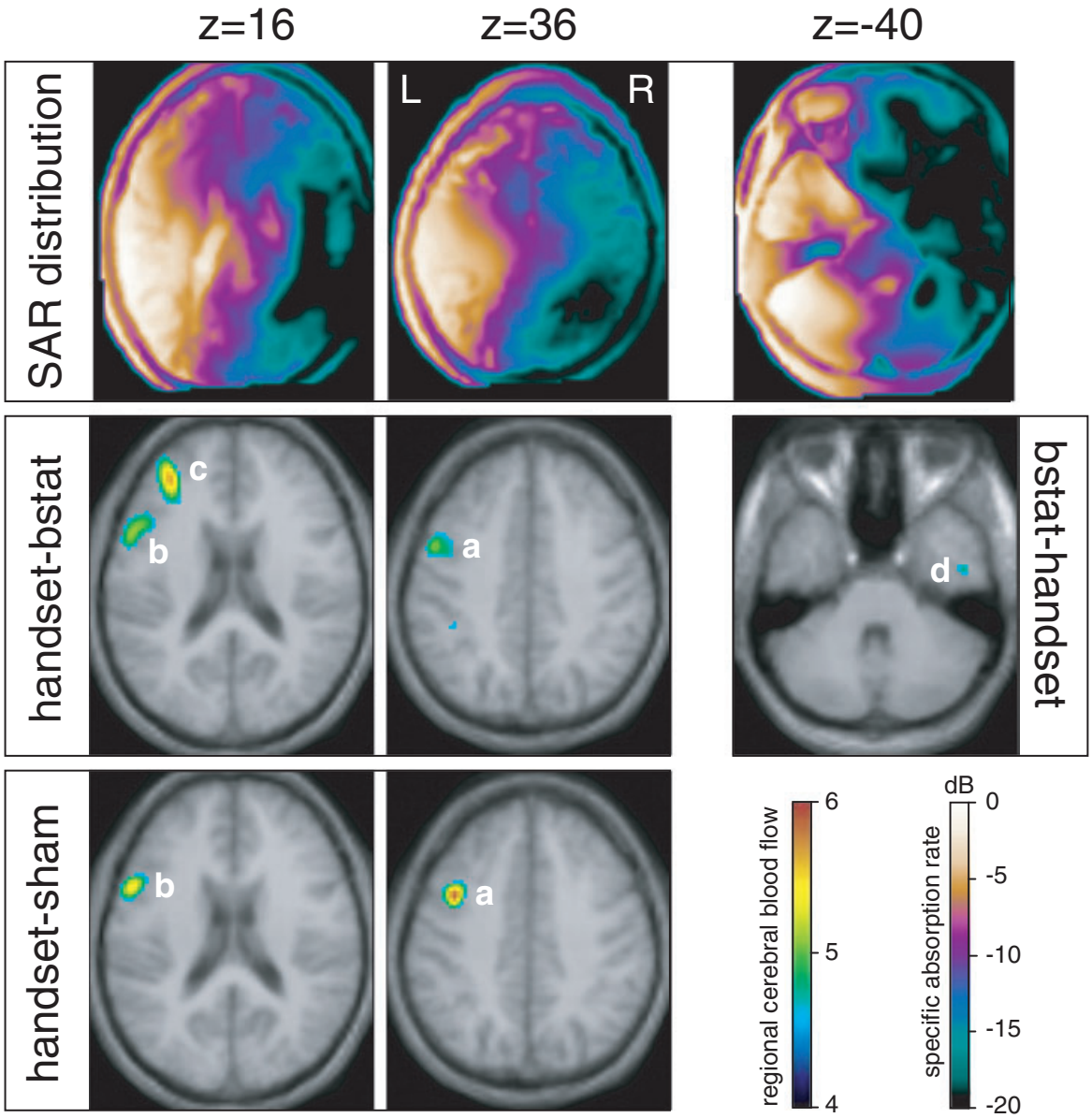

FIG. 2. Computed distribution of the specific absorption rate (SAR). Axial sections were matched with the corresponding PET sections (see below). For details of SAR simulations see Materials and methods. 0 dB (right colour bar) corresponds to a SAR of 1 W/kg. Changes in rCBF after RF EMF exposure. Regions showing higher (*handset–bstat*, *handset–sham, bstat–handset*) relative rCBF after RF EMF exposure assessed by SPM ($n = 12$). *t*-values corrected for multiple comparisons are illustrated (left colour bar). The numbers on top of the columns indicate the horizontal plane of the axial sections (MNI coordinates). *Handset–bstat*, *handset–sham:* $z = 16$ and $z = 40$; *bstat–handset:* $z = -40$. L, left; R, right. The labels a–d indicate the brain regions referred to in Tables 1 and 2.

replication studies failed to confirm changes in cognitive functions (Haarala *et al*., 2003b; Krause *et al*., 2004).

The RF EMF exposure of the left hemisphere for 30 min increased subsequent rCBF in the ipsilateral dorsolateral PFC (Fig. 2; Table 1). The distribution of the SAR within the brain did not reflect the changes in rCBF. Changes in rCBF were observed in areas where exposure was high, however, according to the SAR distribution much larger areas were exposed to a similar degree without showing significant changes in rCBF. This finding further supports a non-thermal action of RF EMF on brain physiology.

In a recent study, Haarala *et al*. (2003a) did not observe changes in rCBF during exposure related to the RF EMF. An active and a sham condition were recorded consecutively in a randomized, cross-over design. In view of the present and previous data (Huber *et al*., 2000, 2002) indicating that RF EMF may induce long-lasting effects, active RF EMF exposure might have contaminated half of the sham recordings and obscured rCBF alterations associated with RF EMF.

The contrast *bstat–handset* revealed only a minor difference in the activation of the cerebellum contralateral to the exposure and the contrast *bstat–sham* revealed no difference. Thus, compared with the handset exposure bstat seems to have limited effects on rCBF. This observation is of interest as handset and bstat signals also differently affected the sleep EEG. After bstat exposure (both exposure during sleep and after exposure prior to sleep) non-REM sleep EEG power in the spindle band was initially increased, an effect that decreased in the course of the sleep episode (Borbély *et al*., 1999; Huber *et al*., 2000).

TABLE 2. VOI analysis

Contrast	Region	BA	Factor *P*-values		
			Hemisphere	Time	Hem*time
Handset–sham					
	a	9	–	–	–
		6	0.0120	–	–
	b	44	0.0001	–	–
Handset–bstat					
	c	10	0.0626	–	–
	a	9	0.0524	–	–
	b	44	0.0001		0.0473
Bstat–handset					
	d	20	0.0007	–	–

P-values of two way ANOVAs ($n = 12$) with factors 'hemisphere' (left or right), 'time' (10, 20 and 30 min after exposure) and the interaction term 'hem*time' (–, not significant, $P > 0.1$). VOI were selected based on *t*-values ≥ 5 from the SPM statistics (see Materials and methods for details). BA = Brodmann area. For abbreviations used to indicate brain regions see Table 1. Individual ratios of the two conditions of the contrast of both hemispheres and all three time points entered the ANOVAs.

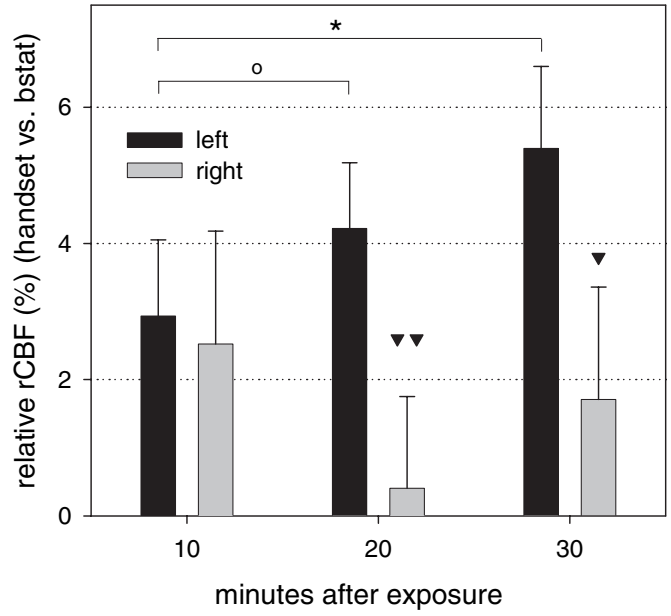

FIG. 3. Time course of the relative regional cerebral blood flow (rCBF) after handset exposure compared with the bstat exposure (= 100%) in the left inferior frontal gyrus (BA 44). Average rCBF data ($n = 12$) in the left and right hemispheres are presented. *Post-hoc* paired *t*-tests showed significant hemispheric differences (triangles, one: $P < 0.05$, two: $P < 0.005$) and a gradual increase in rCBF in the exposed (left) hemisphere across consecutive 10-min intervals (open circle: $P = 0.07$; star: $P < 0.005$).

In contrast, the changes in the spindle range appeared to increase in the course of the night after handset exposure (Huber *et al*., 2002). Interestingly, we found a gradual increase in rCBF within the first 30 min after handset exposure compared with bstat exposure (Fig. 3). In addition, the increase of EEG power during sleep included a broader frequency range after bstat exposure (Borbély *et al*., 1999; Huber *et al*., 2000) than after handset exposure (Huber *et al*., 2002). Thus, inconsistent results in the analysis of event-related brain potentials during RF EMF exposure might be in part related to differences in the modulation paradigms (Eulitz *et al*., 1998; Freude *et al*., 1998; Jech *et al*., 2001).

The strong hemispheric asymmetry in waking rCBF after RF EMF exposure contrasts with the lack of hemispheric asymmetries in the sleep EEG after bi- or unilateral exposure of the cortex (Huber *et al*., 2000, 2003). Because the exposure of the thalamus was similar in both experiments (approx. 0.1 W/kg), it was suggested that the effects during sleep involve subcortical structures and their bilateral projections to the cortex (Huber *et al*., 2003). The discrepancies between waking and sleep might reflect state specific differences in neuronal activation that are possibly related to the different activation level of neuromodulators such as noradrenalin (Cirelli & Tononi, 2000). Whereas cortical activation during waking is strongly dependent on waking behaviour (Vanderwolf, 1992), cortical activity during sleep is dominated by widespread thalamo-cortical and cortico-cortical oscillations underlying EEG slow waves and sleep spindles (Steriade *et al*., 1993). The more global activation pattern during sleep may facilitate EMF stimulation-induced sleep spindle oscillations that emerge from subcortical brain structures (thalamus). After long-term unilateral auditory stimulation during waking, EEG power in the spindle frequency range was increased in subsequent non-REM sleep and no hemispheric asymmetries were observed (Cantero *et al*., 2002). Spindle oscillations were associated with neural network reorganization after learning and/or sensory experience (Sejnowski & Destexhe, 2000). Strong or prolonged cortical activation during waking may therefore induce cortical reorganization during subsequent sleep reflected in changes in spindle oscillations.

A further point for discussion is the relation of the counting task and our observed changes in rCBF. The affected regions of the left dorsolateral PFC play a major role in working memory (Rypma *et al*., 1999; Dade *et al*., 2001; Wagner *et al*., 2001). Moreover, they are also involved in propositional speech production and verbal fluency, but not in counting, as a recent PET study showed (Blank *et al*., 2002). Because the subjects invariably counted in all conditions, the strong activation of the PFC after the handset exposure is not likely to reflect an interaction between the counting task and RF EMF exposure. The counting task was introduced to ensure similar cognitive activity during all conditions in order to avoid spurious activation (Gusnard & Raichle, 2001).

In conclusion, we demonstrated that exposure to pulse-modulated RF EMF alters brain physiology as reflected in regional changes of cerebral blood flow. Furthermore, the modulation paradigm was shown to be critical for RF EMF-induced increase of rCBF in the dorsolateral PFC. However, the observed effects of pulse-modulated RF EMF were subtle and the underlying mechanisms remain unknown. Thus, conclusions about health consequences of RF EMF exposure are premature.

Acknowledgements

This study was supported by the Swiss National Science Foundation, the Human Frontiers Science Program, and the Research Cooperation Sustainable Mobile Communication. We thank Dr Alexander Borbély for comments on the manuscript and Dr Thomas Graf for help with the data collection.

Abbreviations

BA, Brodmann areas; bstat, 'base-station-like'; EEG, electroencephalogram; GSM, global system for mobile communication; handset, 'handset-like' signal; PET, positron emission tomography; PFC, prefrontal cortex; rCBF, regional cerebral blood flow; REM, rapid eye movement; RF EMF, radio frequency electromagnetic fields; SAR, specific absorption rate; SPM, statistical parametric mapping; TMS, transcranial magnetic stimulation; VOI, volume of interest.

References

Blank, S.C., Scott, S.K., Murphy, K., Warburton, E. & Wise, R.J. (2002) Speech production: Wernicke, Broca and beyond. *Brain*, **125**, 1829–1838.

Borbély, A.A., Huber, R., Graf, T., Fuchs, B., Gallmann, E. & Achermann, P. (1999) Pulsed high-frequency electromagnetic field affects human sleep and sleep electroencephalogram. *Neurosci. Lett.*, **275**, 207–210.

Cantero, J.L., Atienza, M., Salas, R.M. & Dominguez-Marin, E. (2002) Effects of prolonged waking-auditory stimulation on electroencephalogram synchronization and cortical coherence during subsequent slow-wave sleep. *J. Neurosci.*, **22**, 4702–4708.

Chen, R., Classen, J., Gerloff, C., Celnik, P., Wassermann, E.M., Hallett, M. & Cohen, L.G. (1997) Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology*, **48**, 1398–1403.

Cirelli, C. & Tononi, G. (2000) Differential expression of plasticity-related genes in waking and sleep and their regulation by the noradrenergic system. *J. Neurosci.*, **20**, 9187–9194.

Croft, R.J., Chandler, J.S., Burgess, A.P., Barry, R.J., Williams, J.D. & Clarke, A.R. (2002) Acute mobile phone operation affects neural function in humans. *Clin. Neurophysiol.*, **113**, 1623–1632.

Dade, L.A., Zatorre, R.J., Evans, A.C. & Jones-Gotman, M. (2001) Working memory in another dimension: functional imaging of human olfactory working memory. *Neuroimage*, **14**, 650–660.

Edelstyn, N. & Oldershaw, A. (2002) The acute effects of exposure to the electromagnetic field emitted by mobile phones on human attention. *Neuroreport*, **13**, 119–121.

Eulitz, C., Ullsperger, P., Freude, G. & Elbert, T. (1998) Mobile phones modulate response patterns of human brain activity. *Neuroreport*, **9**, 3229–3232.

Freude, G., Ullsperger, P., Eggert, S. & Ruppe, I. (1998) Effects of microwaves emitted by cellular phones on human slow brain potentials. *Bioelectromagnetics*, **19**, 384–387.

Friston, K.J., Ashburner, J., Poline, J.B., Frith, C.D., Heather, J.D. & Frackowiak, R.S.J. (1995) Spatial registration and normalisation of images. *Hum. Brain Mapp.*, **2**, 165–189.

Gusnard, D.A. & Raichle, M.E. (2001) Searching for a baseline: functional imaging and the resting human brain. *Nat. Rev. Neurosci.*, **2**, 685–694.

Haarala, C., Aalto, S., Hautzel, H., Julkunen, L., Rinne, J.O., Laine, M., Krause, B. & Hamalainen, H. (2003a) Effects of a 902 MHz mobile phone on cerebral blood flow in humans: a PET study. *Neuroreport*, **14**, 2019–2023.

Haarala, C., Bjornberg, L., Ek, M., Laine, M., Revonsuo, A., Koivisto, M. & Hamalainen, H. (2003b) Effect of a 902 MHz electromagnetic field emitted by mobile phones on human cognitive function: a replication study. *Bioelectromagnetics*, **24**, 283–288.

Huber, R., Graf, T., Cote, K.A., Wittmann, L., Gallmann, E., Matter, D., Schuderer, J., Kuster, N., Borbély, A.A. & Achermann, P. (2000) Exposure to pulsed high-frequency electromagnetic field during waking affects human sleep EEG. *Neuroreport*, **11**, 3321–3325.

Huber, R., Schuderer, J., Graf, T., Jutz, K., Borbély, A.A., Kuster, N. & Achermann, P. (2003) Radio frequency electromagnetic field exposure in humans: estimation of SAR distribution in the brain, effects on sleep and heart rate. *Bioelectromagnetics*, **24**, 262–276.

Huber, R., Treyer, V., Borbély, A.A., Schuderer, J., Gottselig, J.M., Landolt, H.P., Werth, E., Berthold, T., Kuster, N., Buck, A. & Achermann, P. (2002) Electromagnetic fields, such as those from mobile phones, alter regional cerebral blood flow and sleep and waking EEG. *J. Sleep Res.*, **11**, 289–295.

Jech, R., Sonka, K., Ruzicka, E., Nebuzelsky, A., Bohm, J., Juklickova, M. & Nevsimalova, S. (2001) Electromagnetic field of mobile phones affects visual event related potential in patients with narcolepsy. *Bioelectromagnetics*, **22**, 519–528.

Koivisto, M., Krause, C.M., Revonsuo, A., Laine, M. & Hamalainen, H. (2000a) The effects of electromagnetic field emitted by GSM phones on working memory. *Neuroreport*, **11**, 1641–1643.

Koivisto, M., Revonsuo, A., Krause, C., Haarala, C., Sillanmaki, L., Laine, M. & Hamalainen, H. (2000b) Effects of 902 MHz electromagnetic field emitted by cellular telephones on response times in humans. *Neuroreport*, **11**, 413–415.

Krause, C.M., Haarala, C., Sillanmaki, L., Koivisto, M., Alanko, K., Revonsuo, A., Laine, M. & Hamalainen, H. (2004) Effects of electromagnetic field emitted by cellular phones on the EEG during an auditory memory task: a double blind replication study. *Bioelectromagnetics*, **25**, 33–40.

Kuster, N., Balzano, Q. & Lin, J.C. (1997) *Mobile Communications Safety*. Chapman & Hall, London.

Kuster, N., Schuderer, J., Christ, A., Futter, P. & Ebert, S. (2004) Guidance for exposure design of human studies addressing health risk evaluations of mobile phones. *Bioelectromagnetics*, **25**, 524–529.

Mottaghy, F.M., Gangitano, M., Krause, B.J. & Pascual-Leone, A. (2003) Chronometry of parietal and prefrontal activations in verbal working memory revealed by transcranial magnetic stimulation. *Neuroimage*, **18**, 565–575.

Pascual-Leone, A., Valls-Sole, J., Wassermann, E.M. & Hallett, M. (1994) Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain*, **117**, 847–858.

Preece, A.W., Iwi, G., Davies-Smith, A., Wesnes, K., Butler, S., Lim, E. & Varey, A. (1999) Effect of a 915-MHz simulated mobile phone signal on cognitive function in man. *Int. J. Radiat. Biol.*, **75**, 447–456.

Rypma, B., Prabhakaran, V., Desmond, J.E., Glover, G.H. & Gabrieli, J.D. (1999) Load-dependent roles of frontal brain regions in the maintenance of working memory. *Neuroimage*, **9**, 216–226.

SAS Institute Inc (1999) *SAS/STAT User's Guide*. SAS Institute Inc., Cary, NC.

Sejnowski, T.J. & Destexhe, A. (2000) Why do we sleep? *Brain Res.*, **886**, 208–223.

Steriade, M., McCormick, D.A. & Sejnowski, T.J. (1993) Thalamocortical oscillations in the sleeping and aroused brain. *Science*, **262**, 679–685.

Vanderwolf, C.H. (1992) The electrocorticogram in relation to physiology and behavior: a new analysis. *Electroencephalogr. Clin. Neurophysiol.*, **82**, 165–175.

Wagner, A.D., Maril, A., Bjork, R.A. & Schacter, D.L. (2001) Prefrontal contributions to executive control: fMRI evidence for functional distinctions within lateral prefrontal cortex. *Neuroimage*, **14**, 1337–1347.

Wood, J.N. & Grafman, J. (2003) Human prefrontal cortex: processing and representational perspectives. *Nat. Rev. Neurosci.*, **4**, 139–147.